



0181 '99 DEC 27 A9:40

December 22, 1999

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, room 1061  
Rockville, MD 20852

Dear Sirs:

In response to the proposed rule regarding Suitability Determination for Donors of Human Cellular and Tissue-Based Products (published in the Federal Register on September 30, 1999), Advanced Tissue Sciences, Inc., offers the following comments:

1. Provision needs to be made for grandfathering of products currently on the market or in clinical evaluation, particularly if these products are made using previously qualified master cell banks where new donor information can not be obtained and where testing by current methods is not possible because the donor is not available, or their suitability status may have changed. In such cases, testing to standards in place at the time the tissue was obtained and appropriate for the given donor material should supercede the proposed rules with regard to relevant parts of the donor suitability determination.
2. In many cases the donor screening is done by a tissue bank and not by the manufacturer. In such cases, the tissue bank may be unable or unwilling to provide the specific donor information to the user of the product. It is important to include a provision that permits the tissue bank to qualify the donor as suitable and then to certify that suitability to the manufacturer who further processes the cells or tissue. A mechanism should be provided to provide traceability through use of a donor number (rather than donor identification) that will remain in the manufacturer's records and that can be used to trace the cells or tissue to the donor through the tissue bank if necessary.
3. We want to emphasize to the FDA the importance of retaining in the final rule the provision in section 1271.80 that permits testing of an appropriate specimen from the mother of a fetal or neonatal donor, rather than a test of the donor directly.
4. We regard the FDA proposal for differentiating the testing requirements for leukocyte-rich and leukocyte-poor as helpful. We propose adding cultures of certain cell types, such as fibroblasts, to the list of materials that are not considered to be leukocyte-rich..
5. With regard to records of donor suitability determination, when a single cell bank is used to make multiple batches of products it should be specified that a single set of

97N-4845

C184

- records can be referenced for all batches made from the cell bank, and that separate records are not required to be maintained within each batch record.
6. It is important to retain the proposed rule in section 1271.60 that permits, under certain safeguards, shipping of material that is in quarantine.
  7. The definition of relevant medical records (1271.3 (v)) requires inclusion of the physical assessment of a cadaveric donor or the physical examination of a living donor. We feel that these evaluations are of minimal clinical utility for diagnosis of the diseases of concern, particularly if the available exam was not done looking for evidence of specific disease. We are also concerned that this requirement will substantially reduce the available donor pool. We propose that this requirement be moved to the "if available" part of the definition.
  8. It would be appropriate for the FDA to coordinate the donor screening requirements with those of other countries, particularly those that are part of the ICH. Without such coordination, manufacturers who market products internationally will have multiple sets of testing requirements. For instance, the standard screening test for HCV in Europe is a Nucleic Acid Amplification detection method (CPMP/BWP/390/97 - 'The Introduction of Nucleic Acid Amplification (NAT) for the Detection of Hepatitis C Virus RNA in Plasma Pools: Addendum to Note for Guidance on Plasma Derived Medicinal Products'. Operational - 1 July 1999). This is a highly sensitive method that has detected incidence of HCV viral genomes when serological tests have been negative. Sera originally tested only by anti-HCV methods may require re-testing to satisfy European authorities if a US product of biological nature is to gain entry into a European market.

In addition, we previously made comments to the Office of Information and Regulatory Affairs regarding the information collections provisions of the proposed rules. The comments we made are as follows:

We have several concerns about the proposed requirement that manufacturers ship products accompanied by documentation of donor suitability determination, defined as a copy of the donor's medical records, results of testing, and the name and address of the establishment that made the suitability determination. We do not believe that this information is useful to the product end-user if other, more typical, controls are in place to ensure product safety. Additionally, we do not believe this requirement is necessary to accomplish the objective of preventing introduction, transmission, or spread, of communicable diseases. Last, it imposes burdens that have not been considered by the FDA.

1. The recipient of a regulated product should be able to assume its safety, if the product has been received from a legitimate supplier. This is consistent with clinicians' expectations of other FDA-regulated products, wherein responsibility for the "qualification" of starting materials (or qualification of "vendors" of product components) rests with the product manufacturer, under FDA supervision. We doubt that the donor suitability information will be of value to the end-user of the product.

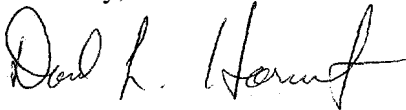
The clinician who prescribes or uses the product cannot be expected to review donor suitability information at the time of product implantation. The donor suitability information should be held by the manufacturer in a manner that allows both forward and backward traceability of donor suitability for products shipped.

2. While the donor suitability labeling provisions of the proposed rule may be appropriate where cells or tissues from a donor go to one or a small number of recipients, where the product must be shipped prior to receipt and evaluation of required test results, or in the limited circumstances where product may be used that was derived from tissues of a donor who is found to be “unsuitable,” this requirement is not necessary or practical for manufactured cell or tissue-based products where a pre-qualified and released master cell bank is the starting material or a component for the finished product. For products based on pre-qualified and released cell banks, standard quality system and cGMP approaches may be employed to assure product safety.
  3. The requirement that donor medical information be widely disseminated may severely restrict the availability of tissue donors. Even if the identity of the donor is masked, the donor or the donor’s next of kin may be reluctant to consent to the donation if they know that personal details of their medical history will be widely distributed.
  4. We propose that in those instances where the product must be shipped before results of testing are received and accepted, or when the material is from an “unsuitable” donor, that a standard required statement should be included in the labeling of all such products, stating the criteria for determination of donor suitability and stating that the criteria have been met.
  5. With regard to records of donor suitability determination, when a single cell bank is used to make multiple batches of products it should be specified that a single set of records can be used for all batches made from the cell bank, and that separate records not be maintained within each batch record. [This is similar to the point made in item 5 in the first section of this letter.]
  6. The definition of relevant medical records (127 1.3 (v)) requires inclusion of the physical assessment of a cadaveric donor or the physical examination of a living donor. We feel that these evaluations are of minimal clinical utility for diagnosis of the diseases of concern, particularly if the available exam was not done looking for evidence of specific disease, and that the requirement will substantially reduce the available donor pool. We propose that this requirement be moved to the “if available” part of the definition. [This is similar to the point made in item 7 in the first part of this letter.]
  7. In summary, the safety of these products should generally be assured by the manufacturers, based on quality systems and cGMP approaches used for other categories of products. More prescriptive measures may be outlined in a “Guideline for Industry” that the Agency could publish and more readily update than a regulation. We disagree that donor-specific information shipped with the product will be of value to the clinician who prescribes or uses the product, and we believe that
-

clinicians will expect the product to meet safety requirements if it has been received from a legitimate manufacturer. In the exceptional cases described in the Supplementary Information and Proposed Rule, donor-specific information, or quarantine status of the product may be appropriate. However, Advanced Tissue Sciences, Inc. would recommend that even in the exceptional cases, a general labeling statement would adequately warn or inform the persons handling the product.

Thank you for your consideration.

Sincerely,

A handwritten signature in black ink, appearing to read "David L. Horwitz". The signature is fluid and cursive, with the first name "David" and last name "Horwitz" clearly distinguishable.

David L. Horwitz, M.D., Ph.D.  
Senior Vice President, Technology